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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,884	07/02/2003	Michael Houghton	PP19545.003	6634

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,884	HOUGHTON, MICHAEL	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *2,3,5-10,19-21,25-40,43,44,46-48 and 50-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,11-18,22-24,41,42,45 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/03; 8/04, 2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.C.D

DETAILED ACTION

1. Applicant's election with traverse of Group V, filed March 28, 2005 is acknowledged. Applicant's arguments have been fully considered regarding the restriction between Groups III-XIII. Upon further consideration of the claimed subject matter and a search of the literature, the restriction requirement between Groups III-V is withdrawn. Claims 2, 3, 13(a), 14(a) and 15 are rejoined. New claims 41, 42 and 45 and 49 are examined. New claims 43, 44, 46-48, and 50-58 are withdrawn from consideration, being drawn to non-elected inventions.

The restriction between Groups VI-XIII is maintained for reasons of record. Applicant argues that a search for all groups encompasses a modified NS3 protein and at least one additional HCV polypeptide. Applicant asserts that such a search would not be overly burdensome. In response to Applicant's arguments, the Examiner has deemed that a search for NS3 with any other HCV would indeed be a serious burden of search. A search for NS3 and any other HCV protein includes a search for multiple proteins (E1, E2, NS1, NS2, NS3, NS4, NS5a, NS5b, core and p7). The Examiner has searched some of these proteins, however, it would be overly burdensome to search and examine all of the HCV proteins in combination with the modified NS3. Therefore, the restriction requirement is deemed proper and made FINAL. In summary, claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 15-18, 22-24, 41, 42 and 45 are examined.

Priority

2. The subject matter of claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 15-18, 22-24, 41, 42 and 45 has priority to provisional applications USSN 60/393,694 and 60/394,510, filed July 2,

2002 and July 8, 2002, respectively. The benefit of priority to USSN 09/721,479 and USSN 60/167,502, filed November 22, 2000 and November 24, 1999, respectively, is denied. The subject matter of the instant claims is drawn to a fusion protein comprising a modified *NS3 polypeptide having an amino acid substitution* that renders the protease of the fusion protein non-functional. The specification of USSN 09/721,479 contemplates the *deletion of NS3* in order to render the protease non-functional. The modifications of deletion and substitution are not the same. Deletion involves the removal of amino acids, while substitution requires the deletion of an amino acid and a replacement amino acid. Therefore, the earliest date to which Applicant may claim priority is July 2, 2002.

Specification

3. The specification is objected to for failing to comply with the sequence rules. The Figures and the Description of the Figures refer to amino acids that have not been referred to by a SEQ ID NO. Also, there is a sequence on page 45, line 21 that lacks a SEQ ID NO. Correction is required.

Claim Objections

4. Claim 12 is objected to because of a minor grammar informality. The phrase, "derived from a different isolate that the modified NS3 polypeptide", should be "derived from a different isolate than the modified NS3 polypeptide".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 17, 18 and 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim 1 and all dependent claims respectively recite, "polypeptide derived from a region of the HCV polyprotein", and "derived from the same HCV isolate", and "derived from a different isolate". These phrases are unclear because the term, "derived" does not impart any clear or definite meaning to the polypeptide. The metes and bounds of the polypeptide from a region of the HCV polyprotein or isolate cannot be determined because Applicant has not set forth the parts that are retained from the original HCV polyprotein or isolate from which the polypeptide is derived. It is suggested that the term in question be deleted.

Claims 13(a), 13(b), 14(a), 14(b), 17, 18, 23 and 24 are drawn to an immunogenic fusion protein consisting essentially of various elements. It is unclear what the metes and bounds of the claims are. Specifically, "consisting essentially of" is considered closed language, open only to elements that do not materially affect the product. The claims, in parts (a) and (b), allow for a variable number of substitutions: His-1083, Asp-1105 and/or Ser-1165. It is unclear how closed language allows for a variable number of amino acid substitutions that affect the product.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Grakoui *et al.* (*J. Virology*, May 1993, 67(5):2832-2843, "Grakoui"). Claim 15 is drawn to a modified NS3 polypeptide comprising a substitution of an amino acid corresponding to His-1083, Asp-1105 and/or Ser-1165, numbered relative to the full-length HCV-1 polyprotein, such that protease activity is inhibited when the modified NS3 polypeptide is present in an HCV fusion protein.

Grakoui discloses the substitution of alanine for His-1083, Asp-1107 and Ser-1165 in HCV NS3, resulting in uncleaved NS domains. This activity qualifies as inhibited protease activity (abstract). While the substitution of alanine for Asp-1107 is not Asp-1105 (as claimed), position 1107 corresponds to the HCV-1 polyprotein, thus meeting the limitation of the claim. With regard to the limitation pertaining to the NS3 polypeptide being present in an HCV fusion protein and having inhibited activity, Grakoui's modified NS3 polypeptide(s) is expected to have inhibited activity when present in a fusion protein. Inhibited activity is expected because Grakoui found that the modified NS3 does not cleave other non-structural polypeptides, and Grakoui found that NS3 is not dependent on NS2 for its protease activity (abstract). The location (within a fusion protein) of the modified NS3 is not expected to change its inhibited protease activity due to the amino acid substitution of His-1083, Asp-1107 or Ser-1165. Therefore, the claim is anticipated by Grakoui.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 11, 12, 13(a), 13(b), 14(a), 14(b), 15-18, 22-24, 41, 42, 45 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paliard *et al.* (WO 01/30812 A2, "Paliard") in view of Houghton *et al.* (US 5,371,017, "Houghton") and Grakoui.

The claims are drawn to an immunogenic fusion protein comprising:

(a) a modified NS3 polypeptide comprising at least one amino acid substitution to the HCV NS3 region, such that protease activity is inhibited, and

(b) at least one polypeptide derived from a region of the HCV polyprotein other than the NS3 region.

The modified NS3 polypeptide comprises a substitution of an amino acid corresponding to His-1083, Asp-1105 and/or Ser-1165, numbered relative to the full-length HCV-1 polyprotein. The fusion protein additionally comprises an NS4 polypeptide, an NS5a polypeptide, an NS5b polypeptide, and optionally a core polypeptide. The modified NS3 polypeptide and the other polypeptide are from the same HCV isolate, or from different isolates. The order of the proteins in the fusion protein from amino to carboxy terminal is: modified NS3 polypeptide, NS4 and NS5a. Another order is modified NS3 polypeptide, NS4, NS5a and NS5b. Another combination is modified NS3 polypeptide, NS4, NS5a and optionally, core polypeptide. Another combination is modified NS3 polypeptide, NS4, NS5a, NS5b and optionally, core polypeptide. Also claimed are compositions comprising the fusion proteins described, in combination with a pharmaceutically acceptable excipient. Also claimed are methods of producing a composition comprising combining the immunogenic fusion protein with a pharmaceutically acceptable

excipient. Claims 41, 42, 45 and 49 are drawn to compositions that optionally are comprised of core polypeptide, wherein the core polypeptide comprises the sequence of amino acid depicted at amino acid position 1772-1892 of SEQ ID NO: 6.

Paliard discloses a method for activating HCV-specific T cells using fusion proteins comprising from two to ten or more polypeptides: HCV NS3, NS4, NS5a, NS5b and core polypeptides (abstract and page 17, lines 22-25). The core region of the HCV polyprotein occurs at amino acid positions 1-191 of HCV polyprotein numbered relative to HCV-1. The order of NS3, NS4, NS5a and NS5b occurs in any order in the fusion protein, as well as polypeptides from HCV various strains (page 16, 16-20, and page 17, lines 7-21). Paliard also discloses the use of the fusion proteins in compositions that additionally comprise pharmaceutically acceptable carriers (page 22-23, bridging paragraph). Paliard fails to teach an amino acid substitution(s) in the NS3 polypeptide rendering the protease (NS3) inhibited. Paliard further fails to teach the specific substitutions.

However, Houghton teaches that the replacement of critical residue, serine, in the active site of the NS3 (protease) does not significantly alter the structure of the protease, and thus preserves binding specificity. Houghton teaches that the substituted protease retains its recognition and binding properties while failing to effect cleavage of the polyprotein (col. 3, lines 29-34, and col. 14, lines 32-48). With regard to the specific substitution, Grakoui discloses the substitution of alanine for His-1083, Asp-1107 and Ser-1165 in HCV NS3, resulting in uncleaved NS domains. This activity qualifies as inhibited protease activity (abstract). While the substitution of alanine for Asp-1107 is not Asp-1105 (as claimed), position 1107 corresponds to the HCV-1 polyprotein, thus meeting the limitation of the claim.

It would have been obvious to incorporate Houghton's teachings and Grakoui's teachings into the fusion protein of Paliard. One would have been motivated to render the protease (NS3) non-functional in order to avoid cleavage of polyprotein, as taught by Houghton (col. 3, lines 29-34, and col. 14, lines 32-48). One would have been motivated to substitute the amino acids taught by Grakoui because Houghton discloses that certain substitutions result in the inhibition or ablation of protease function. One would have had a reasonable expectation that Paliard's fusion protein would have worked with Houghton's NS3 amino acid substitution and Grakoui's substitution, because Grakoui demonstrates that the substitutions result in inhibited or non-existent protease activity. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

8. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen

Stacy B. Chen
June 8, 2005